



The Neural Circuit Characteristics of Repetitive Transcranial Magnetic Stimulation Over The Dorsolateral Prefrontal Cortex for The Treatment of Migraine*

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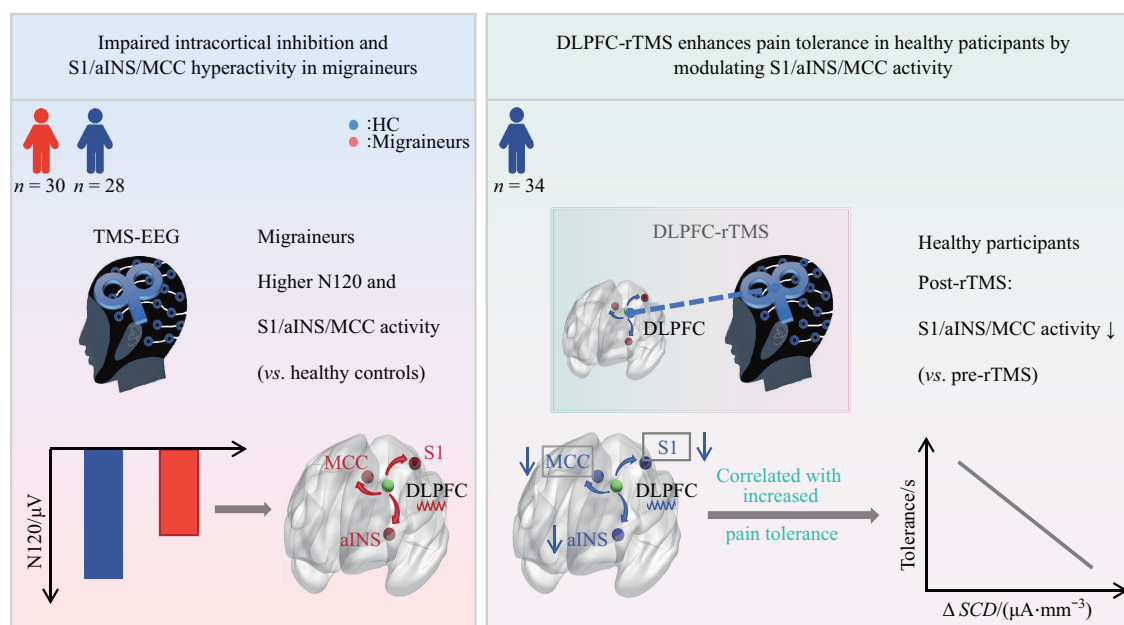
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Graphical abstract



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Abstract Objective Migraine is a leading neurological disorder and the fourth most common cause of years lived with disability worldwide, affecting nearly 116 million individuals. Although pharmacological treatments are available, their efficacy is often limited by side effects and variable response rates. Repetitive transcranial magnetic stimulation (rTMS) over the dorsolateral prefrontal cortex (DLPFC) offers a safe, non-invasive alternative for migraine management. However, the neurophysiological mechanisms, particularly how rTMS modulates local cortical excitability and distributed pain-related circuits, remain poorly understood. Elucidating these mechanisms is essential for optimizing treatment protocols and improving clinical outcomes. **Methods** This study employed concurrent transcranial magnetic stimulation and electroencephalography (TMS-EEG) to investigate neuroplastic and neurocircuitry mechanisms of DLPFC-rTMS in migraine. Study 1 compared 30 migraineurs and 28 healthy controls to identify abnormalities in TMS-evoked potentials (TEPs) and significant current density (SCD) within sensory-discriminative regions including the primary somatosensory cortex (S1) and posterior insula (pINS), cognitive-affective regions including the anterior insula (aINS) and midcingulate cortex (MCC), and a descending modulatory region, the periaqueductal gray (PAG). Study 2 used a single-blind, crossover, sham-controlled design in 34 healthy participants. Each participant received both active (10 Hz, 80% RMT, 1 500 pulses) and sham DLPFC-rTMS in counterbalanced order. TMS-EEG and cold pain tolerance were assessed before and after each session. **Results** In Study 1, migraineurs showed a significantly less negative N120 amplitude compared to healthy controls ($P=0.027$, Cohen's $d=0.60$), indicating local intracortical disinhibition. No group differences were observed for N40, P60, or P180 components. At the source level, migraineurs exhibited significantly higher SCD in the S1, pINS, aINS, and MCC (all $Q<0.05$), but not in the ventroposterior thalamus (vpTHAL), mediodorsal thalamus (mdTHAL), or PAG. In Study 2, active rTMS significantly reduced SCD from pre- to post-stimulation in the S1, aINS, and MCC (all $Q<0.05$). Sham stimulation also reduced SCD in the S1 ($Q<0.05$) but not in the aINS or MCC. Although no significant group-level analgesic effect was observed between active and sham conditions ($P=0.107$), correlation analyses revealed that greater SCD reductions in the S1 and MCC were significantly associated with higher post-rTMS pain tolerance ($R=-0.487$ and -0.495 , both $Q<0.01$) and larger improvements in pain tolerance ($R=-0.487$ and -0.451 , both $Q<0.05$). No such correlations were found following sham stimulation, suggesting that the behavioural relevance of neural changes is specific to active rTMS. **Conclusion** This study provides novel evidence that migraineurs exhibit both local neuroplastic abnormalities (reduced N120 amplitude) and hyperactivity in key pain-processing regions (S1, pINS, aINS, MCC). A single session of DLPFC-rTMS reduced hyperactivity in the aINS, MCC, and S1. Notably, greater reductions in the S1 and MCC were associated with improved pain tolerance. These findings identify distinct cortical circuitries, particularly within the cognitive-affective pain network, that may serve as potential biomarkers for optimizing rTMS treatment in migraine and other chronic pain conditions. Future studies should validate these results in patient populations experiencing spontaneous migraine attacks and explore multi-session or accelerated rTMS protocols.

Key words migraine, TMS, DLPFC, TMS-EEG

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Migraine is characterized by recurrent moderate to severe pulsating headaches^[1]. According to the Global Burden of Diseases (GBD), nearly 116 million individuals suffer from migraine, making it the fourth leading cause of years lived with disability worldwide^[2-3]. In addition to medications, other treatment options are being developed to reduce migraine frequency and intensity. Repetitive transcranial magnetic stimulation (rTMS) is a safe and non-invasive form of brain stimulation technology. By targeting the dorsolateral prefrontal cortex (DLPFC), a few studies have demonstrated a positive effect of rTMS on migraine conditions^[4-6]. Our group has recently synthesised rTMS effects on migraine and identified a clear mid-term benefit (1–6 weeks follow-up). However, there was a significant variance in treatment response. In addition, the long-term benefits of rTMS were not clear for migraineurs^[7]. These findings together highlight the necessity to optimise treatment efficacy for migraineurs.

Understanding the mechanisms of action represents an important strategy to improve rTMS

treatment response and long-term benefits for migraine. Accumulating evidence suggests that migraine is associated with abnormalities in central nervous system plasticity, which are characterized by adaptive and maladaptive changes at both synaptic and neural circuit levels^[8-9]. Neurophysiological studies have identified abnormal cortical excitability and synaptic plasticity dysfunction in patients with migraine^[10]. Structural imaging studies have demonstrated cortical thickness changes in pain-processing regions such as the somatosensory cortex and insula^[11]. Animal experiments have further confirmed that modulating synaptic plasticity can effectively alleviate migraine-related pain^[12]. Together, these findings indicate that neuroplasticity abnormalities represent one of the core features of migraine pathophysiology. These plastic changes not only constitute the pathological basis for recurrent migraine attacks, but may also serve as potential targets for the therapeutic effects of rTMS. However, the mechanisms by which rTMS exerts its effects in patients with migraine remain largely unexplored.

Only a few studies have explored the mechanisms underlying rTMS in migraineurs. Using functional magnetic resonance imaging (fMRI), DLPFC-rTMS was found to increase functional connectivity between the frontal cortex and somatosensory and cingulate cortices^[13]. Another study demonstrated that DLPFC-rTMS increased connectivity between the frontal and temporal channels with electroencephalography (EEG)^[14]. These two studies suggest a mechanism of pain modulation in migraineurs.

Nevertheless, migraineurs are characterised by complex and distributed network abnormalities, extending from sensory and emotional pain experience networks^[15-16], to pain-related attention and modulation systems^[17-18]. Existing rTMS studies have only begun to reveal certain circuit-level effects. Specifically, functional fMRI, while offering excellent spatial resolution, lacks sufficient temporal resolution to capture dynamic changes in neural activity. EEG, though providing millisecond-level temporal resolution, offers limited spatial information. Therefore, an approach that integrates high temporal resolution with adequate spatial resolution is essential for comprehensively investigating pain-related networks in patients with migraine. Concurrent TMS-EEG enables simultaneous assessment of neuroplasticity and neurocircuitry changes with millisecond-level temporal resolution, allowing for spatiotemporal tracking of stimulation-evoked activity. TMS-evoked potentials (TEPs) offer an effective assessment of local cortical excitability following rTMS^[19-20]. In addition, TMS-EEG is able to capture current propagation from the target to distributed regions^[21-23], such that SCD calculates the current density of a cortical region beyond the surface regions. These technical advantages enable TMS-EEG to characterize the spatiotemporal dynamics of rTMS effects on multi-network abnormalities in patients with migraine.

Using TMS-EEG, the current study was designed to systematically uncover the neuroplastic and neurocircuitry mechanisms of rTMS in migraineurs. We initially revealed the neuroplastic and neurocircuitry abnormalities in migraineurs compared to healthy controls. We further went on to examine whether rTMS could restore these abnormalities as well as their role in pain experiences. We expected to see the abnormalities and treatment effects across the sensory and emotional pain networks, as well as pain-related attention and modulation systems.

1 Materials and methods

1.1 Participants

Study 1 recruited both migraineurs and healthy controls. A power analysis was conducted using G*Power^[24]. Group differences in current density between chronic pain and healthy controls were specified to compute the sample size, which ranged from 0.68 to 0.78 in pain processing and modulation structures^[25]. Power analysis indicated 28 participants in each group ($\alpha=0.05$, $\text{power}=0.80$, Cohen's $d=0.68$). A total of 30 migraineurs (age range: 18–63 years; mean $\pm$ SD: (38.20 $\pm$ 13.52) years; 26 females) were recruited from the Affiliated Hospital of Hangzhou Normal University. The inclusion criteria were: (1) diagnosis of migraine according to the International Classification of Diseases, 11th Revision (ICD-11)^[26]; (2) aged ≥ 15 years; (3) no medication adjustments during or within 2 weeks preceding the study; (4) ability to complete clinical assessments and rTMS treatment; (5) willingness to participate with a signed informed consent. The minimum age threshold was set at 15 years to accommodate adolescent migraine sufferers, though ultimately no participants under 18 were enrolled in this study. The exclusion criteria were: (1) contraindications to TMS (*e. g.*, cardiac pacemakers, intracranial metal implants, epilepsy history, or pregnancy); (2) severe psychiatric disorders (Hamilton Depression Rating Scale score ≥ 35 or Hamilton Anxiety Rating Scale Score ≥ 29); (3) aphasia or cognitive impairment (Mini-Mental State Examination Score ≤ 23); (4) history of neurosurgery; (5) severe cardiopulmonary dysfunction, extreme debilitation, or other unstable clinical conditions.

A total of 28 healthy, right-handed, TMS-eligible adults (age range: 18–63 years; mean $\pm$ SD: (40.7 $\pm$ 14.5) years; 23 females) were recruited to match the gender and age of migraineurs^[27]. Independent sample *t*-test indicated no significant difference in age between groups ($t(56)=0.68$, $P=0.516$). Chi-square test with Yates' continuity correction showed no significant difference in gender distribution ($\chi^2(1)=0.013$, $P=0.910$), confirming that the two groups were well matched for age and gender. Exclusion criteria included a current or past psychiatric diagnosis or psychotropic medication use, assessed *via* the Mini-International Neuropsychiatric Interview (MINI)^[28]. Both the migraineurs and healthy controls provided a written informed consent. This study was approved by

the Ethics Committee of Hangzhou Normal University Affiliated Hospital (2022E2HS027) and conducted in accordance with the Declaration of Helsinki.

Study 2 enrolled 36 healthy participants with the same inclusion and exclusion criteria of healthy controls as study 1. Two participants withdrew after the first session due to unwillingness to continue, and data from 34 participants were analysed (age range: 18–25 years; mean±SD: (20.85±2.03) years; 20 females). All participants provided written informed consent. Study 2 received ethical approval from the Centre for Cognition and Brain Disorders at Hangzhou Normal University (20201218) and adhered to the Declaration of Helsinki.

1.2 Experimental design and procedures

In study 1, single-pulse TMS-EEG was used to assess neuroplastic and neurocircuitry responses in both migraineurs and healthy controls. Study 2 was a single-blind, crossover, and sham-controlled design. Participants completed two laboratory visits (interval≥72 h; mean±SD: (7.34±6.05) d) where they received left DLPFC and sham stimulation in a pseudo-randomised, counterbalanced order. Single-pulse TMS-EEG was administered to the left DLPFC pre- and post-rTMS. A cold pain protocol was also performed before and after each session (Figure 1). All the methods were the same in these two studies unless specified.

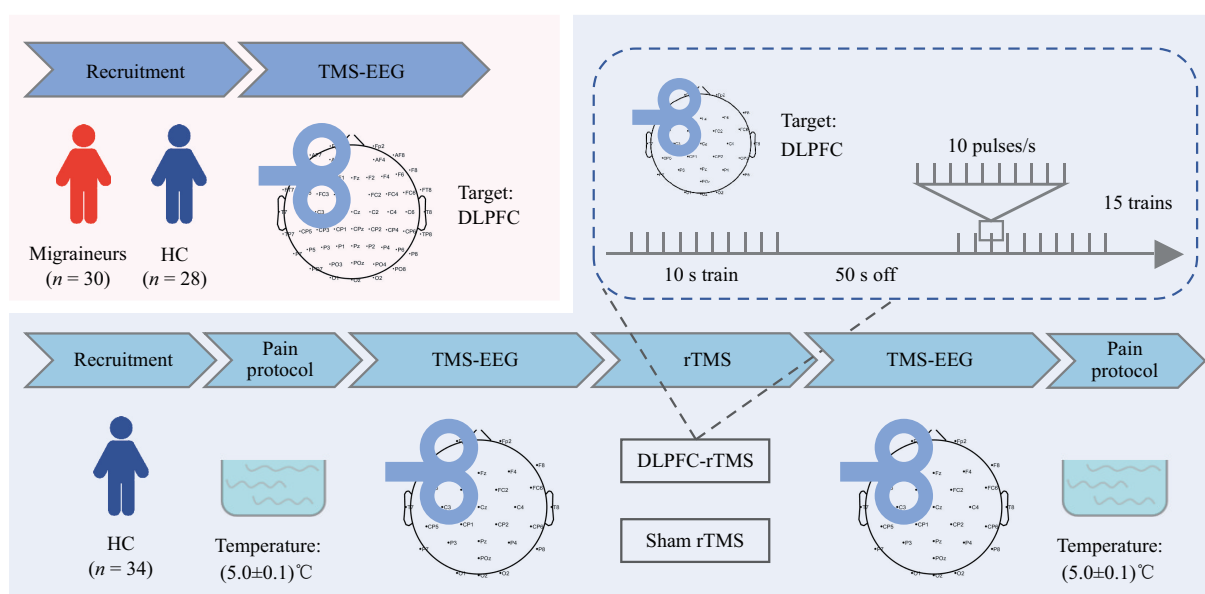


Fig. 1 Schematic diagram of the overall study workflow

Red areas indicate the experimental workflow of study 1, while blue areas represent the workflow of study 2. HC: healthy controls.

1.3 Resting motor threshold (RMT) and single-pulse TMS-EEG

RMT was defined as the minimum intensity to induce motor-evoked potentials (MEPs) >50 μ V in the first dorsal interosseous (FDI) muscle in 5/10 consecutive trials. Single-pulse TMS was delivered to the left M1 hand area (45° from midline) via a Magstim Rapid² system connected to a figure-of-eight coil. To facilitate consistency, RMT determination was conducted after EEG setup. Coil placement was measured relative to nasion andinion for cross-session reproducibility in study 2^[29-31].

The DLPFC was targeted using the Beam F3 algorithm^[32], which estimates the scalp coordinates of the left DLPFC based on the international 10–20 system without requiring individual structural MRI.

While this approach offers relatively lower spatial precision than neuronavigation, it ensures consistent and reproducible targeting across participants and sessions^[29, 31]. Single-pulse TMS was then delivered to the left DLPFC using the following parameters: 105 pulses at 110% RMT, with the coil positioned perpendicular to the midline (handle pointing left) using a figure-of-eight coil.

White noise masking was applied via earplugs until participants reported minimal auditory perception of TMS clicks^[33-34]. The interstimulus intervals were 5 s±10% jitter.

1.4 EEG recording

During single-pulse TMS, EEG was recorded in a temperature-controlled, sound-attenuated, and electrically shielded room. Participants remained

seated with eyes open and fixated forward. For study 1, a 64-channel EEG system (Brain Products GmbH, Germany) was used for continuous recording at 5 000 Hz, with FCz as the reference and AFz as the ground electrode. Electrode impedances were maintained below 5 k Ω throughout the session. Study 2 used the same EEG system but with a 32-channel setup.

1.5 Cold pain assessment

The cold pressor test has been commonly used in rTMS studies^[31, 35-36]. In this study, participants immersed their dominant right hand in a computer-controlled circulating cold-water bath at (5.0 $\pm$ 0.1) $^{\circ}$ C (dhc-0505-a, <http://www.qiweiyiqi.com/>)^[37-38]. As expectation could impact pain perception^[39-40], a standardised conditioning procedure was implemented to familiarise participants with the stimulus intensity and minimise anticipatory effects. Participants first immersed their non-dominant hand in the cold-water bath for 30 s^[37-38]. During this period, they were instructed to verbally describe the cold sensation (e.g., “cool” “cold” “painful”) but no pain ratings were recorded. Following a 5 min drying and rest period, formal testing commenced with the dominant hand. Participants were instructed to withdraw their hand when they could no longer tolerate the cold pain. Pain tolerance was defined as the time interval from complete palmar immersion to voluntary withdrawal.

1.6 Repetitive transcranial magnetic stimulation

In study 2, rTMS was delivered to the left DLPFC at an intensity of 80% RMT^[41-42]. The rTMS protocol consisted of 15 trains of 10 s stimulation at 10 Hz frequency, with 50 s inter-train intervals (totalling 1 500 pulses)^[41, 43]. Sham stimulation followed the same protocol, with the coil being flipped 90 $^{\circ}$ angle relative to the scalp to direct the magnetic field away from the head^[44].

1.7 TMS-EEG data processing and analysis

TMS-EEG data were pre-processed using the TMS-EEG signal analyser (TESA)^[20, 45], and custom scripts running on MATLAB platform (R2017b, the MathWork, USA). A fully automated pipeline was used to avoid bias^[45]. Data were initially epoched around the TMS pulses (–1 000 to 1 000 ms) and baseline corrected (–500 to –10 ms). The large magnetic pulses were then removed and interpolated (–5 to 20 ms). Data were then downsampled to 1 000 Hz and visually inspected for bad epochs or channels.

A first round of FastICA was performed to remove decay artifacts (signal in 11–35 ms > 4 times of signal in 30–1 000 ms) using the TESA toolbox^[45]. Data were then filtered using Butterworth filters

(band-pass=1–100 Hz; band-stop=48–52 Hz). A second round of FastICA was performed to remove non-neural artifacts: eye blinks (components where the weightings from FP1 and FP2 were >2.5 times of other electrodes), lateral eye movements (weightings of F7 and F8 were $\pm$ 2 times of other electrodes), persistent muscle activity (components where the slope of the log-log power spectrum fitted between 7 and 70 Hz, excluding 48–52 Hz, was >–0.31), and electrode noise (absolute Z-score of one or more electrodes >4)^[45]. Component rejections were performed using automated heuristics followed by visual inspection by two experienced researchers blinded to group assignment. Removed channels were interpolated, and the data were re-referenced to the common average.

After pre-processing, TMS-EEG data was analysed with sensor level amplitude indicated as TEPs and source activity indicated as SCD. In sensor level analyses, EEG channel lying over the TMS target was selected (F5, AF3). An a priori analysis was conducted on N120 (95–135 ms). This TEP component was selected as it is most consistently modulated by rTMS^[46-48]. It is also considered as the most robust TEP component with the greatest signal-to-noise ratio^[49-50]. The other three TEPs were also explored (N40: 35–45 ms; P60: 45–65 ms; P180: 165–205 ms).

In SCD analysis, a boundary element headmodel (BEM) was used according to a standard 10–20 template aligned with EEG electrode locations used in this study. The three compartments (scalp, skull, brain) were assigned conductivity values of 0.33 S/m, 0.004 1 S/m, and 0.33 S/m, respectively, following standard settings in TMS-EEG source modelling^[22, 45]. A source grid model was then defined with 8-mm spacing, which balances spatial resolution with computational efficiency and is consistent with previous TMS-EEG studies^[22, 45].

Source activities were calculated by a linearly constrained minimum variance (LCMV) beamformer. SCD is a standardised measure of regional excitability induced by TMS^[21]. It is calculated with the following equation: $SCD = \sum_{x \in s} \sum_{t \in \sigma} SS(x, t) * |J_{norm}(x, t)|$. $SS(x, t)$ is the significant sources across the brain at each time point, and J_{norm} is the averaged post-pulse time series at source level, normalised by subtracting the mean pre-pulse value and dividing by pre-pulse variances.

Both study 1 and study 2 examined seven regions of interest (ROIs) selected to represent three key functional dimensions of pain processing. Sensory-

discriminative regions included S1, vpTHAL, and pINS. Cognitive-affective regions comprised mdTHAL, aINS, and MCC. The descending modulatory dimension was represented by PAG. This selection aligns with conceptualizations of pain as involving distributed hierarchical processing^[51].

1.8 Statistical analysis

Statistical analyses were performed in SPSS (version 25; IBM Corp.). Independent sample *t*-tests were used to compare TEP and SCD data between migraineurs and healthy controls in study 1. Meanwhile, paired *t*-tests compared SCD data in pre- and post-rTMS in study 2. To examine the analgesic effects of DLPFC-rTMS, change scores of pain tolerance were calculated from pre- to post-rTMS for each condition, and a paired *t*-test was used to compare DLPFC with sham condition. Pearson correlations were used to examine correlations between TMS-EEG and pain data. To control for multiple comparisons across tests, the false discovery rate (FDR) correction was applied. Statistical significance for all analyses was determined based on the FDR-corrected *Q* value, with a threshold of *Q* <

0.05 (two-tailed).

2 Results

2.1 Demographic and clinical information

This migraine cohort had disease duration ranging from 1 month to 50 years, with a mean of approximately 11.2 years. Over the past three months, the monthly headache frequency had an average of about 15 d per month, and the mean headache intensity score (assessed by 0–10 numerical rating scale, NRS) was approximately 6.4 points. Most of the latest headache episodes occurred within 1 to several days before the study assessment. The healthy controls had no history of migraine or related treatment.

2.2 Local neuroplastic abnormalities in migraineurs (study 1)

Grand-averaged TEP waveforms are shown in Figure 2. Migraineurs had a less negative N120 amplitude compared to healthy controls in the DLPFC ($t(56) = 2.27$, $P = 0.027$, Cohen's $d = 0.60$). No other effects were observed in N40, P60, or P180 ($P = 0.210$, $P = 0.113$, $P = 0.092$).

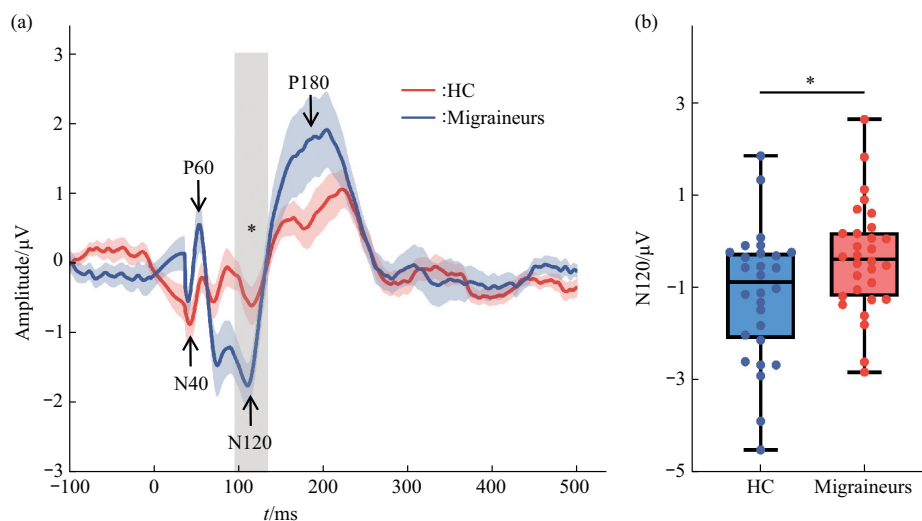


Fig. 2 Local neuroplastic abnormalities in migraineurs in study 1

(a) Grand-averaged TEP waveforms from the two groups. Migraineurs had a less negative N120 amplitude compared to healthy controls (HC) in the DLPFC (95–135 ms). (b) The average and individual data of N120. * $P < 0.05$.

2.3 Neural circuitry abnormalities in migraineurs (study 1)

In the time window of N120, migraineurs showed significantly higher SCD than healthy controls in the S1 ($t(56) = 3.68$, $P = 0.001$, Cohen's $d = 0.97$, $Q = 0.004$), pINS ($t(56) = 3.02$, $P = 0.004$, Cohen's $d = 0.79$, $Q = 0.013$), aINS ($t(56) = 2.58$, $P = 0.013$, Cohen's $d = 0.68$, $Q = 0.026$), and MCC ($t(56) = 2.52$, $P =$

0.015, Cohen's $d = 0.66$, $Q = 0.026$) (Figure 3a, c, e, f). No significant group differences were observed in the vpTHAL, mdTHAL, or PAG (all $Q > 0.05$, Figure 3b, d, g).

2.4 Neural circuitry changes induced by DLPFC-rTMS (study 2)

In the time window of N120, DLPFC-rTMS significantly decreased SCD from pre- to post-rTMS

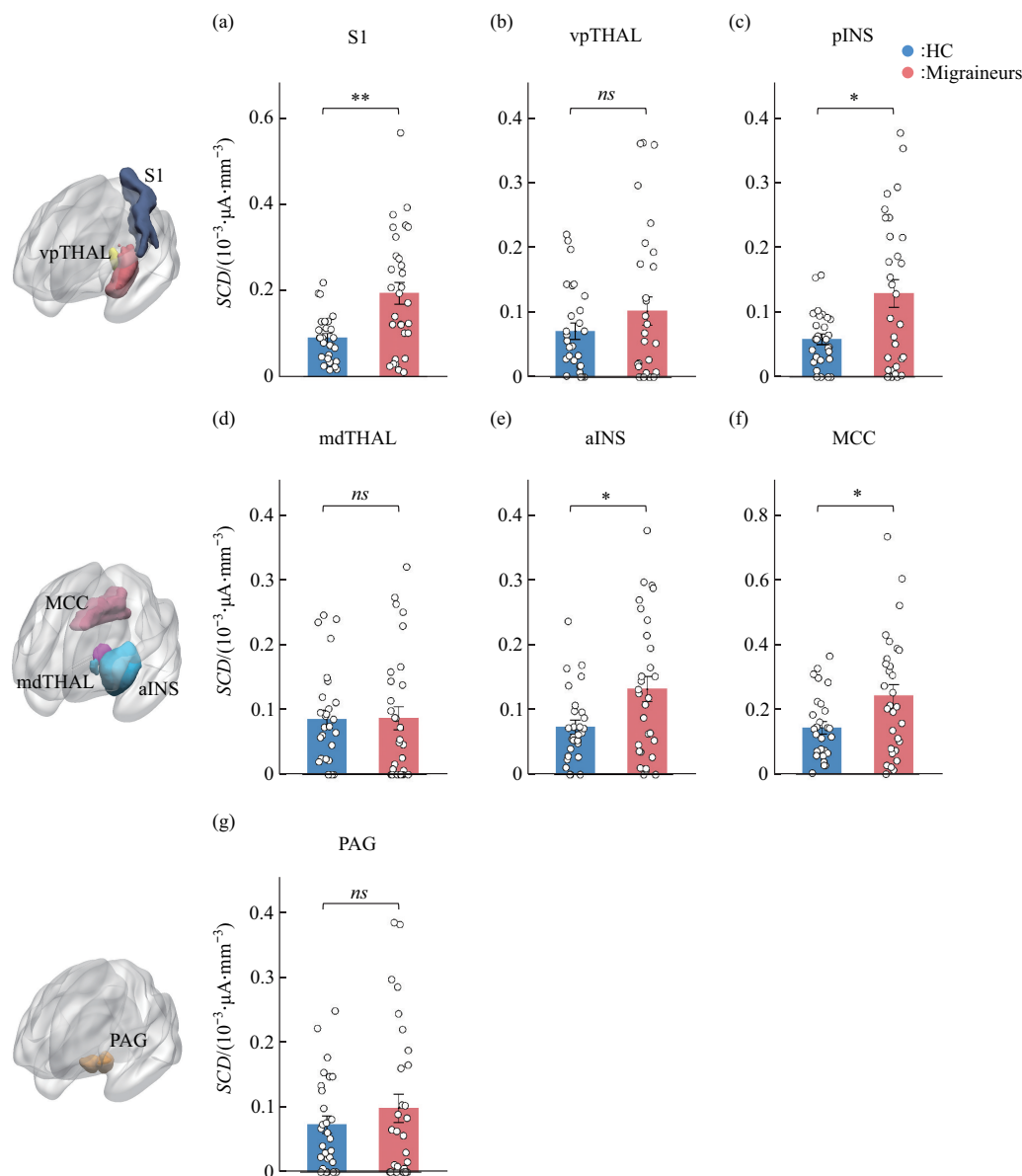


Fig. 3 SCD comparisons between the migraineurs and healthy controls in study 1

(a–c) SCD comparisons in the sensory-discriminative regions (S1, vpTHAL and pINS). Migraineurs showed higher SCD than healthy controls (HC) in the S1 and pINS. (d–f) SCD comparisons in the cognitive-affective regions (mdTHAL, aINS and MCC). Migraineurs also showed higher SCD than healthy controls (HC) in the aINS and MCC. (g) SCD comparisons in the descending structure (PAG). All *P*-values are FDR-corrected. **Q*<0.05, ***Q*<0.01, *ns* not significant.

in the S1 ($t(33)=-2.87$, $P=0.007$, Cohen's $d=0.49$, $Q=0.025$), aINS ($t(33)=-2.70$, $P=0.011$, Cohen's $d=0.46$, $Q=0.026$), and MCC ($t(33)=-2.99$, $P=0.005$, Cohen's $d=0.51$, $Q=0.025$) (Figure 4a, e, f). Following sham stimulation, significant decreases in SCD were observed in the S1 ($t(33)=-2.93$, $P=0.006$, Cohen's $d=0.50$, $Q=0.022$) and mdTHAL ($t(33)=-3.24$, $P=0.003$, Cohen's $d=0.56$, $Q=0.020$) (Figure 4a, d). No significant changes were found in the vpTHAL, pINS, or PAG (all $Q>0.05$, Figure 4b, c, g).

2.5 Pain perception and correlations with neural circuitry changes (study 2)

Group comparison revealed no significant difference in the increase in pain tolerance between DLPFC- and sham-rTMS ($t(33)=1.66$, $P=0.107$). Similarly, analysis of the proportional change ((post-pre)/pre) also showed no significant difference between the two conditions ($t(33)=0.680$, $P=0.501$).

Correlation analyses revealed that decreased SCD in the S1 was associated with both higher pain

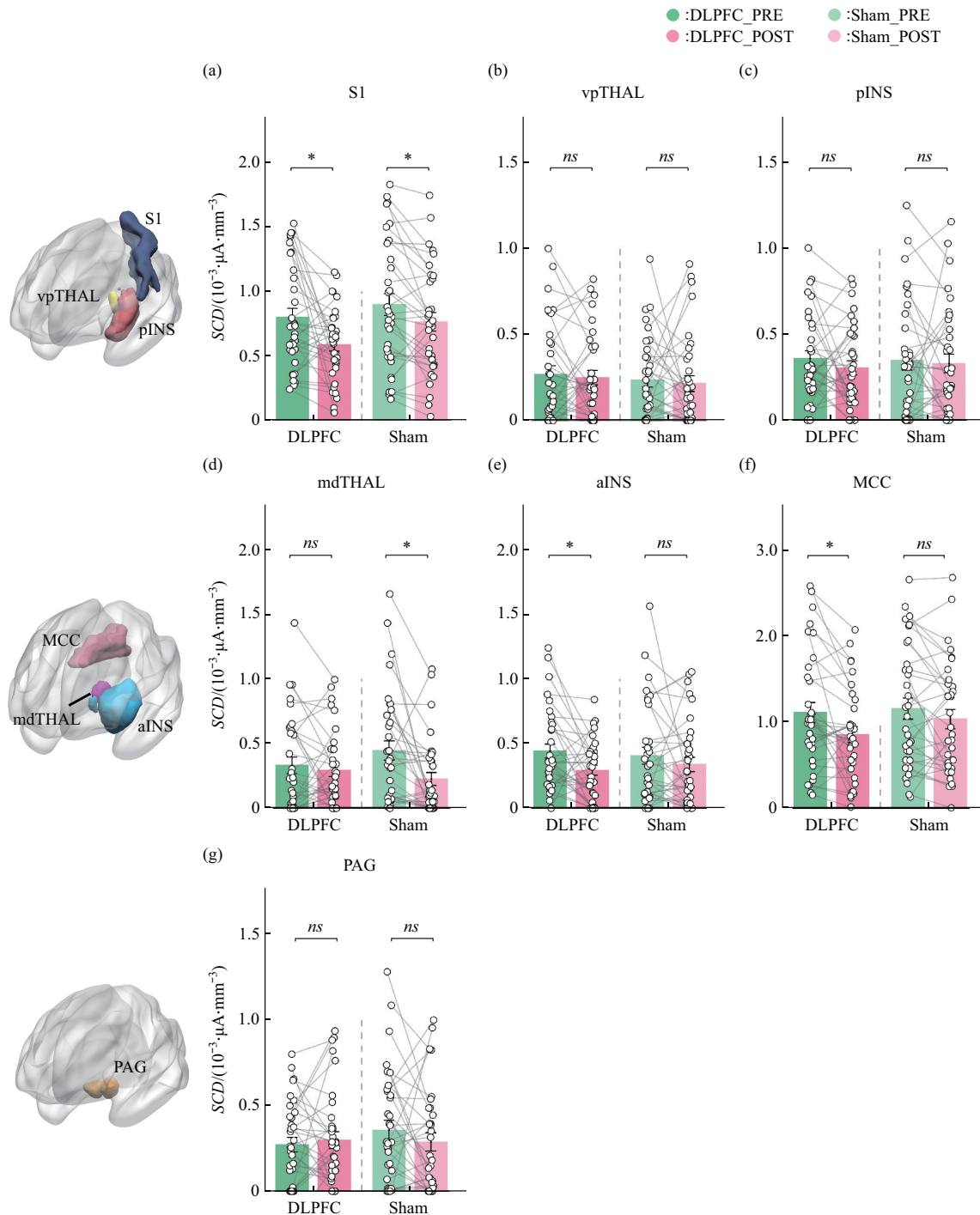


Fig. 4 SCD comparisons between pre- and post-rTMS in study 2

(a–c) SCD comparisons in the sensory-discriminative regions (S1, vpTHAL and pINS). DLPFC-rTMS decreased SCD in the S1 from pre- to post-rTMS. (d–f) SCD comparisons in the cognitive-affective regions (mdTHAL, aINS and MCC). DLPFC-rTMS also selectively decreased SCD in the aINS and MCC from pre- to post-rTMS. (g) SCD comparisons in the descending structure (PAG). All P -values are FDR-corrected. * $Q < 0.05$, ** $Q < 0.01$, ns not significant.

tolerance at post-rTMS ($R = -0.487$, $P = 0.004$, $Q = 0.005$) and a greater increase in pain tolerance from pre- to post-rTMS ($R = -0.487$, $P = 0.004$, $Q = 0.011$) (Figure 5a, b). Similarly, decreased SCD in the MCC

correlated with higher post-rTMS pain tolerance ($R = -0.495$, $P = 0.003$, $Q = 0.005$) and a greater increase in pain tolerance across the stimulation period ($R = -0.451$, $P = 0.007$, $Q = 0.011$) (Figure 5c, d). In contrast,

following sham stimulation, decreased SCD in the S1 showed no significant correlation with either post-

rTMS pain tolerance ($R=0.220$, $P=0.212$) or the increase in pain tolerance ($R=-0.124$, $Q=0.484$).

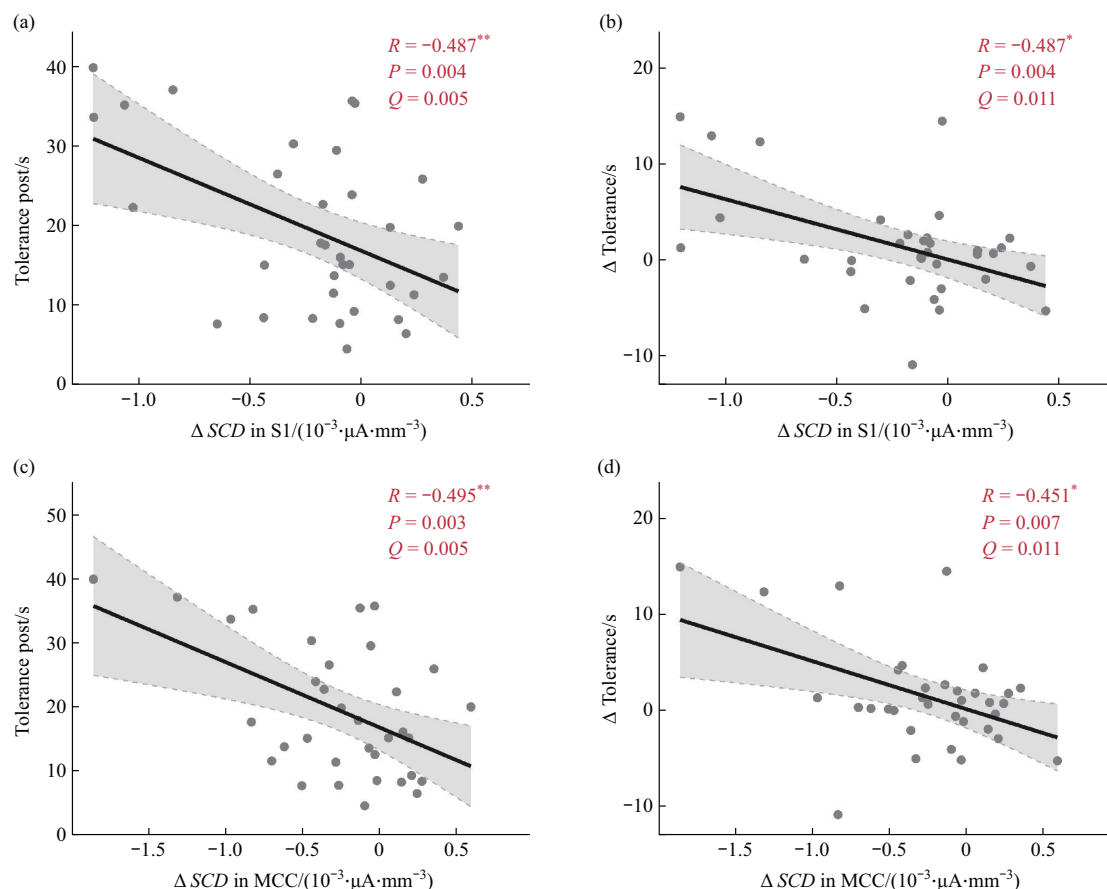


Fig. 5 Decreased SCD in the S1 and MCC correlates with pain tolerance in study 2

The figure shows negative correlations between the reduction in source current density (ΔSCD , post-pre) and pain tolerance metrics. (a) Correlation between ΔSCD in the S1 and post-rTMS pain tolerance. (b) Correlation between ΔSCD in the S1 and the improvement in pain tolerance ($\Delta Tolerance$, post-pre). (c) Correlation between ΔSCD in the MCC and post-rTMS pain tolerance. (d) Correlation between ΔSCD in the MCC and $\Delta Tolerance$. All P -values are FDR-corrected. * $Q < 0.05$, ** $Q < 0.01$.

3 Discussion

With concurrent TMS-EEG technology, we provide novel findings that migraineurs are characterised by a less negative N120 amplitude compared to healthy controls. TEPs are a series of negative and positive components induced by single TMS pulses. Among them, N120 has the highest signal-to-noise ratio, which is considered to reflect GABAB-mediated intracortical inhibition^[52-54]. Our findings thus indicate impaired intracortical inhibition in migraineurs. This extends a previous meta-analysis which identified a disinhibition in neuropathic pain conditions^[55]. In addition, this finding is consistent with fMRI data that migraineurs had abnormal connections in the executive control network in which

the DLPFC is a key node^[18, 56].

Notably, this impairment of intracortical inhibition exhibited temporal specificity. In contrast to the N120 abnormality, no significant differences were observed between migraine patients and healthy controls in the N40, P60, or P180 components. N40 is primarily considered to reflect fast cortical inhibition mediated by GABAA receptors, P60 is associated with glutamatergic excitatory activity, and P180 has been linked to voltage-gated sodium channels^[52, 54, 57]. In contrast, N120 reflects slow-time-course cortical inhibition mediated by GABAB receptors, which is critically involved in the long-term regulation of synaptic plasticity^[58]. The selective abnormality of the N120 component in migraine patients suggests that the underlying pathophysiology may be more closely

related to impaired slow-time-course inhibition rather than alterations in other aspects of cortical excitability.

At the source level, in line with DLPFC disinhibition, migraineurs also demonstrated higher current density in the S1, pINS, aINS, and MCC in our data. This set of ROIs involves processes from sensory encoding to affective-cognitive evaluation in pain processing. S1 and pINS, as core sensory processing areas, showed hyperactivity^[51]. Their hyperactivity is neurobiologically consistent with the widespread hypersensitivity and exaggerated response to noxious stimuli commonly observed in migraineurs. Furthermore, hyperactivity was also observed in the affective-cognitive hubs of the pain network. The aINS, closely linked to interoceptive abnormalities and anxiety in chronic pain, and the MCC, a core region encoding pain unpleasantness and regulating attentional resources toward pain^[59], both displayed abnormal excitability. This helps explain why migraine extends beyond sensory symptoms to encompass significant emotional distress and cognitive burden^[60]. Our finding of MCC hyperactivity aligns with prior evidence of its heightened responsiveness to noxious stimuli in individuals with migraine^[61]. Notably, a study reported no difference in IC/MCC activation under standard noxious stimuli between migraineurs and

healthy controls, brainstem trigeminal nucleus activity showed periodic predictive changes^[59]. In contrast, the hyperactivity observed at the source level for aINS/pINS/MCC in this study provides new evidence for cortical homeostatic imbalance in migraineurs. Within this framework, our results suggest that the reduced inhibitory function in the DLPFC may impair its top-down regulation over these hyperactive sensory and affective integration nodes, potentially contributing to a deficient endogenous analgesic system.

After identifying the S1, pINS, aINS, and MCC hyperactivity in migraineurs, our data further demonstrated that DLPFC stimulation selectively decreased current density in the aINS and MCC in a group of healthy participants. Our previous study demonstrated that DLPFC stimulation induced local excitability changes that were associated with an analgesic effect^[62]. In migraineurs, DLPFC-rTMS treatment was further found to increase functional connectivity between the DLPFC and somatosensory and cingulate cortices^[13]. Building on these findings, the current study identified neuroplastic changes in circuitries that likely underlie the analgesic effects of DLPFC stimulation. A theoretical summary of this neuroplasticity and neurocircuitry mechanism is provided in Figure 6. These novel and consistent findings provide circuitry evidence for the

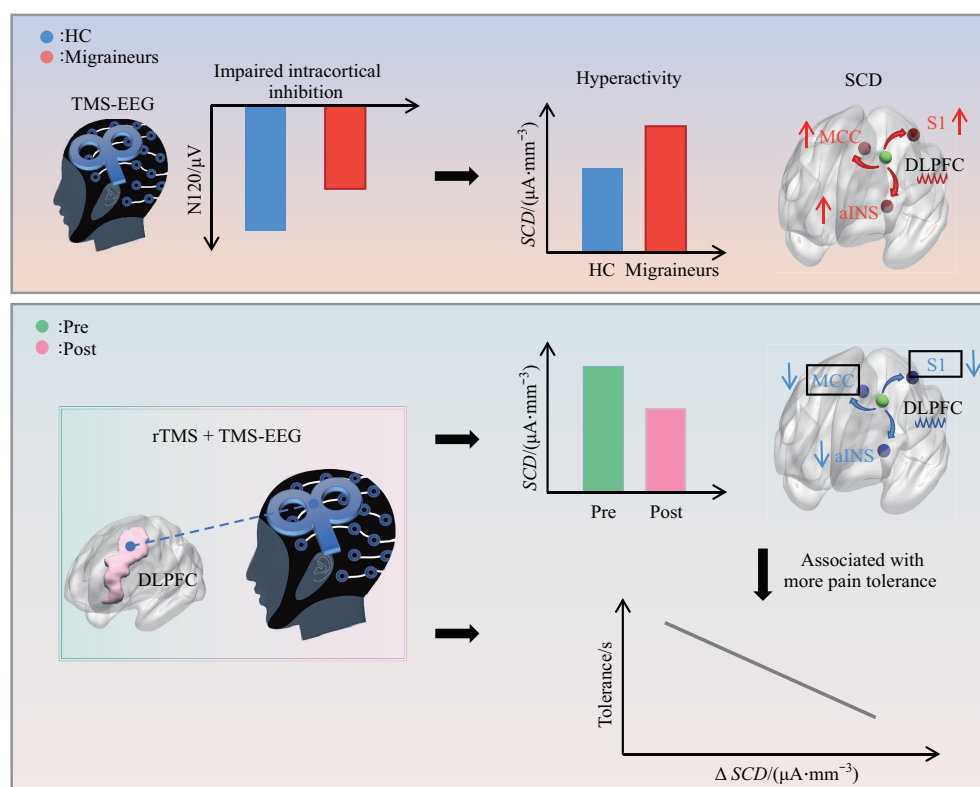


Fig. 6 Theoretical summary of DLPFC-rTMS induced neuroplasticity and neurocircuitry modulation in migraine

Arrows indicate TMS-evoked SCD changes (DLPFC→aINS/MCC/S1) supported by the present data. HC: healthy controls.

optimisation of rTMS efficacy for migraineurs and potentially other chronic pain conditions (discussed later).

Indeed, we provided further evidence that decreased current density in the S1 and MCC was associated with both greater pain tolerability at post-rTMS and a larger improvement in tolerability (post-pre) after DLPFC stimulation. This finding helps build up connections between brain activity changes and pain experiences. As a key node integrating sensory and affective information and involved in cognitive control^[61], the correlation observed in the MCC suggests that rTMS analgesia may operate in part by improving the cognitive-affective evaluation of pain. Concurrently, the reduction in S1 activity indicates that the therapeutic effect also involves modulation of primary sensory representation. Therefore, DLPFC-rTMS may exert potential analgesic effects by synergistically regulating sensory processing and cognitive-affective evaluation networks.

To determine whether the observed neural-behavioural associations were specific to active stimulation, we further analysed neural changes under sham stimulation. We found that sham stimulation induced a significant decrease in SCD in the S1 and mdTHAL. Notably, sham stimulation did not induce significant SCD changes in the MCC. Therefore, it is important to demonstrate whether the association between S1 and pain tolerance is unique to active stimulation. To address this, we further calculated the correlations between sham-induced neural changes (in the S1 and mdTHAL) and behavioural changes. The results showed no statistically significant correlations. This dissociation observed in the S1 indicates that the behavioural relevance of a neural change is distinct from its mere occurrence. These sham-induced neural changes could arise from multiple factors. Although we used white noise masking to control auditory input^[63], sham stimulation still produces genuine somatosensory input and participant expectation and placebo effects^[64]. These non-specific factors are sufficient to activate core sensory pathways including the thalamus and S1, giving rise to measurable neural responses^[65].

We also found no significant difference in pain perception between real and sham stimulation ($P=0.107$). However, real DLPFC stimulation increased pain tolerance (1.37), whereas sham stimulation did not (-0.36). Several factors may account for these null behavioural findings. One possibility is that behavioural changes require more treatment sessions than neural changes, particularly in healthy

individuals. Moreover, healthy volunteers have intact pain processing, leaving limited room for modulation, and the cold pressor test may have limited sensitivity to single-session rTMS. Together with the neural-level findings, this discrepancy suggests that neuroplastic changes may precede behavioural improvements or require repeated sessions to accumulate.

It is worth noting that the pINS, which showed hyperactivity in migraineurs (study 1), was not significantly modulated by a single session of DLPFC-rTMS in healthy participants (study 2). This discrepancy likely reflects regional differences in sensitivity to DLPFC-rTMS. Functionally, the pINS is specialised for multimodal integration of sensory pain features, contributing to stable and sustained somatic perception^[66]. Structurally, aINS is strongly connected to the ventral prefrontal cortex (*e.g.*, BA45/47) *via* the uncinate fasciculus, while the pINS predominantly connects to sensorimotor regions with sparse prefrontal projections^[67-68]. Functional connectivity studies further support this distinction. A TMS-fMRI study demonstrated that 10 Hz rTMS over the left DLPFC reliably activates the aINS as part of the salience network^[69]. Moreover, resting-state functional connectivity studies have shown that baseline connectivity between the DLPFC and the aINS predicts clinical response to rTMS in patients with major depressive disorder^[70], further supporting the functional importance of this pathway. In contrast, the pINS is more strongly coupled with sensorimotor networks and shows weaker integration with prefrontal cognitive control systems. Thus, in the present study, DLPFC-rTMS may have preferentially engaged its interaction with the affective-cognitive network (aINS) while failing to effectively mobilise its regulatory pathway to the sensory integration node (pINS).

Unlike the prominent findings in sensory and affective-cognitive dimensions, no significant SCD changes were observed in the PAG in either migraine patients (study 1) or following rTMS intervention (study 2). Several factors may account for this null finding. First, the PAG is located in the brainstem, relatively distant from the stimulation coil, and a single session of rTMS may be insufficient to induce detectable changes. Second, SCD reflects local neuronal activity elicited by the TMS pulse, *i.e.*, the immediate cortical response to stimulation of the DLPFC. As a core hub of the descending pain modulatory system, the PAG may exert its influence more at the level of functional connectivity than local evoked responses, consistent with previous studies showing altered PAG functional connectivity with

cortical pain networks in migraine^[71]. Thus, the absence of PAG changes does not preclude its involvement in migraine pathophysiology, but suggests that its dysfunction may be more readily captured at the network level. Future studies employing higher stimulation intensities or combined functional connectivity analyses are warranted to further elucidate its role in rTMS analgesia.

Our findings have direct implications for the management of migraineurs and other chronic pain conditions with brain stimulation technologies. Recent studies indicate that connectivity-based TMS targeting may be advantageous in the treatment of depression^[72-74]. This idea has also been proposed for pain management in two review studies^[75-76]. The current study identified unique pain-related circuitries in the aINS and MCC. These novel findings could be utilised to improve treatment efficacy for chronic pain conditions. In addition, rTMS treatment protocols need to be optimised to achieve a better treatment efficacy, such as the development of accelerated TMS paradigms in depression^[77-80]. Our findings thus provide biomarkers for the development of rTMS protocols and parameters to achieve a better analgesic efficacy.

It is noted that study 2 used the cold pressor test to elicit acute, experimentally controlled pain in healthy participants rather than spontaneous migraine attacks. While this paradigm is a widely accepted experimental pain model with high reproducibility^[81], it does not fully simulate the complex pathophysiology of spontaneous migraine. Nevertheless, the cold pressor test activates core pain processing regions, including the insula, cingulate cortex, prefrontal cortex, and somatosensory cortex^[82], which show substantial overlap with regions exhibiting functional abnormalities in migraine patients^[83], as well as with the abnormal brain regions identified in study 1 (*i. e.*, S1, pINS, aINS, MCC). Thus, the mechanisms revealed in healthy individuals may provide insights into the analgesic effect in migraine.

There were some limitations in this study. The two studies differed in study populations (patients with migraine *vs.* healthy controls), age ranges (18–63 years *vs.* 18–25 years), and EEG systems (64-channel *vs.* 32-channel). Given that cortical plasticity changes across the lifespan^[84], age may influence neurophysiological responses to rTMS. However, the age range in both studies falls within the typical onset period of migraine^[85]. A 32-channel EEG can be used in TMS-EEG studies^[86-88], with source localisation accuracy being comparable to higher-density arrays

when using standard head models and predefined regions of interest^[89-90]. It is noted that our conclusions are drawn from qualitative convergence rather than quantitative comparisons between 2 channel arrays. However, future studies are warranted to directly validate these findings in patient populations experiencing spontaneous migraine attacks and with more consistent methodological designs.

Nonetheless, it is worth noting that later TEP components (>100 ms) could be contaminated by artefact in TMS-EEG recordings, which typically have large amplitudes and are generally located over central electrodes^[91-92]. Our N120 component was selected from the frontal cortex with small amplitudes (<2 μ V), and is therefore less affected by such artefacts. In addition, this study focused on pain experience and modulation systems, which may conceal alternative contributions from other brain regions or networks. Future studies could explore these possibilities using data-driven whole-brain approaches^[93], as well as other emerging brain stimulation paradigms to further broaden the therapeutic landscape^[94-95].

4 Conclusion

Migraineurs demonstrated abnormal N120 amplitude over the prefrontal cortex that likely indicates intracortical disinhibition. We also demonstrated hyperactivities in the aINS and MCC in migraineurs, that could be decreased by a single session of DLPFC stimulation. These novel findings together identify neural circuitries that could guide the development of more effective treatment strategies for migraineurs.

Date Availability The datasets generated and analysed during the current study are not publicly available due to the need to protect the privacy and confidentiality of research participants, as the informed consent obtained did not include provisions for open data sharing. However, anonymised data may be available from the corresponding author on reasonable request, subject to approval from the institutional ethics committee.

References

- [1] Wijeratne T, Grisold W, Dodick D, *et al.* World Brain Day 2019: migraine, the painful truth. *Lancet Neurol*, 2019, **18**(10): 914
- [2] Cen J, Wang Q, Cheng L, *et al.* Global, regional, and national burden and trends of migraine among women of childbearing age from 1990 to 2021: insights from the Global Burden of Disease

- Study 2021. *J Headache Pain*, 2024, **25**(1): 96
- [3] GBD 2021 Nervous System Disorders Collaborators. Global, regional, and national burden of disorders affecting the nervous system, 1990-2021: a systematic analysis for the Global Burden of Disease Study 2021. *Lancet Neurol*, 2024, **23**(4): 344-381
 - [4] Sahu A K, Sinha V K, Goyal N. Effect of adjunctive intermittent theta-burst repetitive transcranial magnetic stimulation as a prophylactic treatment in migraine patients: a double-blind sham-controlled study. *Indian J Psychiatry*, 2019, **61**(2): 139-145
 - [5] Todorov V, Bogdanova D, Tonchev P, *et al.* Repetitive transcranial magnetic stimulation over two target areas, sham stimulation and topiramate in the treatment of chronic migraine. *Comptes Rendus De L'académie Bulg Des Sci*, 2020, **73**(9): 1307-1313
 - [6] Brighina F, Piazza A, Vitello G, *et al.* rTMS of the prefrontal cortex in the treatment of chronic migraine: a pilot study. *J Neurol Sci*, 2004, **227**(1): 67-71
 - [7] Zhou J, Wang Y, Luo X, *et al.* Revisiting the effects of rTMS over the dorsolateral prefrontal cortex on pain: an updated systematic review and meta-analysis. *Brain Stimul*, 2024, **17**(4): 928-937
 - [8] Puledda F, Viganò A, Sebastianelli G, *et al.* Electrophysiological findings in migraine may reflect abnormal synaptic plasticity mechanisms: a narrative review. *Cephalalgia*, 2023, **43**(8): 3331024231195780
 - [9] Bian J, Wang X L, Yin L, *et al.* PVN^{CRF} neurons regulate migraine-like allodynia by activating CRFR2 on spinal trigeminal caudalis glutamatergic neurons. *Adv Sci (Weinh)*, 2026, **13**(29): e20530
 - [10] Nardone R, Tezzon F. Short latency trigemino-sternocleidomastoid response in patients with migraine. *J Neurol*, 2003, **250**(6): 725-732
 - [11] Chaudhry B A, Younis S, Messina R, *et al.* Cortical thickness studies in migraine: current evidence and future directions. *Cephalalgia*, 2025, **45**(6): 3331024251341204
 - [12] El-Mezayen N S, Noah A A, El-Ganainy S O. Intranasal empagliflozin modulates synaptic plasticity in migraine: insights into calcium signaling and epigenetic regulation. *Eur J Pharm Sci*, 2025, **213**: 107251
 - [13] Vaninetti M, Lim M, Khalaf A, *et al.* fMRI findings in MTBI patients with headaches following rTMS. *Sci Rep*, 2021, **11**(1): 9573
 - [14] Song P, Li S, Shao Y, *et al.* High frequency-rTMS of the left DLPFC relieve headaches and enhance frontal-temporal connectivity in migraine. *Clin Neurophysiol*, 2025, **173**: 166-172
 - [15] Mathur V A, Khan S A, Keaser M L, *et al.* Altered cognition-related brain activity and interactions with acute pain in migraine. *Neuroimage Clin*, 2015, **7**: 347-358
 - [16] Coppola G, di Renzo A, Petolicchio B, *et al.* Increased neural connectivity between the hypothalamus and cortical resting-state functional networks in chronic migraine. *J Neurol*, 2020, **267**(1): 185-191
 - [17] Krimmel S R, DeSouza D D, Keaser M L, *et al.* Three dimensions of association link migraine symptoms and functional connectivity. *J Neurosci*, 2022, **42**(31): 6156-6166
 - [18] Coppola G, di Renzo A, Petolicchio B, *et al.* Aberrant interactions of cortical networks in chronic migraine: a resting-state fMRI study. *Neurology*, 2019, **92**(22): e2550-e2558
 - [19] Chung S W, Lewis B P, Rogasch N C, *et al.* Demonstration of short-term plasticity in the dorsolateral prefrontal cortex with theta burst stimulation: a TMS-EEG study. *Clin Neurophysiol*, 2017, **128**(7): 1117-1126
 - [20] Rogasch N C, Thomson R H, Farzan F, *et al.* Removing artefacts from TMS-EEG recordings using independent component analysis: importance for assessing prefrontal and motor cortex network properties. *Neuroimage*, 2014, **101**: 425-439
 - [21] Casali A G, Casarotto S, Rosanova M, *et al.* General indices to characterize the electrical response of the cerebral cortex to TMS. *Neuroimage*, 2010, **49**(2): 1459-1468
 - [22] Han S, Li X X, Wei S, *et al.* Orbitofrontal cortex-hippocampus potentiation mediates relief for depression: a randomized double-blind trial and TMS-EEG study. *Cell Rep Med*, 2023, **4**(6): 101060
 - [23] Hadas I, Sun Y, Lioumis P, *et al.* Association of repetitive transcranial magnetic stimulation treatment with subgenual cingulate hyperactivity in patients with major depressive disorder: a secondary analysis of a randomized clinical trial. *JAMA Netw Open*, 2019, **2**(6): e195578
 - [24] Faul F, Erdfelder E, Buchner A, *et al.* Statistical power analyses using G*Power 3.1: tests for correlation and regression analyses. *Behav Res Meth*, 2009, **41**(4): 1149-1160
 - [25] Huang Z, Wang Y, Yan Y, *et al.* Identifying neural circuitry abnormalities in neuropathic pain with transcranial magnetic stimulation and electroencephalogram co-registration. *Neurotherapeutics*, 2025, **22**(2): e00496
 - [26] Treede R D, Rief W, Barke A, *et al.* A classification of chronic pain for ICD-11. *Pain*, 2015, **156**(6): 1003-1007
 - [27] Rossi S, Hallett M, Rossini P M, *et al.* Screening questionnaire before TMS: an update. *Clin Neurophysiol*, 2011, **122**(8): 1686
 - [28] Sheehan D V, Lecrubier Y, Sheehan K H, *et al.* The validity of the Mini International Neuropsychiatric Interview (MINI) according to the SCID-P and its reliability. *Eur Psychiatry*, 1997, **12**(5): 232-241
 - [29] Rogasch N C, Thomson R H, Daskalakis Z J, *et al.* Short-latency artifacts associated with concurrent TMS-EEG. *Brain Stimul*, 2013, **6**(6): 868-876
 - [30] Chung S W, Rogasch N C, Hoy K E, *et al.* Impact of different intensities of intermittent theta burst stimulation on the cortical properties during TMS-EEG and working memory performance. *Hum Brain Mapp*, 2018, **39**(2): 783-802
 - [31] Che X, FitzGibbon B M, Ye Y, *et al.* Characterising the optimal pulse number and frequency for inducing analgesic effects with motor cortex rTMS. *Brain Stimul*, 2021, **14**(5): 1081-1083
 - [32] Beam W, Borckardt J J, Reeves S T, *et al.* An efficient and accurate new method for locating the F3 position for prefrontal TMS applications. *Brain Stimul*, 2009, **2**(1): 50-54
 - [33] Rocchi L, Ibáñez J, Benussi A, *et al.* Variability and predictors of response to continuous theta burst stimulation: a TMS-EEG study. *Front Neurosci*, 2018, **12**: 400
 - [34] Rocchi L, di Santo A, Brown K, *et al.* Disentangling EEG responses to TMS due to cortical and peripheral activations. *Brain Stimul*, 2021, **14**(1): 4-18

- [35] Lefaucheur J P, Drouot X, Ménard-Lefaucheur I, *et al.* Motor cortex rTMS in chronic neuropathic pain: pain relief is associated with thermal sensory perception improvement. *J Neurol Neurosurg Psychiatry*, 2008, **79**(9): 1044-1049
- [36] Summers J, Johnson S, Pridmore S, *et al.* Changes to cold detection and pain thresholds following low and high frequency transcranial magnetic stimulation of the motor cortex. *Neurosci Lett*, 2004, **368**(2): 197-200
- [37] Rainville P, Feine J S, Bushnell M C, *et al.* A psychophysical comparison of sensory and affective responses to four modalities of experimental pain. *Somatosens Mot Res*, 1992, **9**(4): 265-277
- [38] Mitchell LA, MacDonald R A R, Brodie E E. Temperature and the cold pressor test. *J Pain*, 2004, **5**(4): 233-237
- [39] Wager T D, Rilling J K, Smith E E, *et al.* Placebo-induced changes in fMRI in the anticipation and experience of pain. *Science*, 2004, **303**(5661): 1162-1167
- [40] Vase L, Robinson M E, Verne N G, *et al.* Increased placebo analgesia over time in irritable bowel syndrome (IBS) patients is associated with desire and expectation but not endogenous opioid mechanisms. *Pain*, 2005, **115**(3): 338-347
- [41] Nahmias F, Debes C, de Andrade D C, *et al.* Diffuse analgesic effects of unilateral repetitive transcranial magnetic stimulation (rTMS) in healthy volunteers. *Pain*, 2009, **147**(1/2/3): 224-232
- [42] Ciampi de Andrade D, Mhalla A, Adam F, *et al.* Repetitive transcranial magnetic stimulation induced analgesia depends on N-methyl-D-aspartate glutamate receptors. *Pain*, 2014, **155**(3): 598-605
- [43] de Andrade D C, Mhalla A, Adam F, *et al.* Neuropharmacological basis of rTMS-induced analgesia: the role of endogenous opioids. *Pain*, 2011, **152**(2): 320-326
- [44] Pascual-Leone A, Tormos J M, Keenan J, *et al.* Study and modulation of human cortical excitability with transcranial magnetic stimulation. *J Clin Neurophysiol*, 1998, **15**(4): 333-343
- [45] Rogasch N C, Biabani M, Mutanen T P. Designing and comparing cleaning pipelines for TMS-EEG data: a theoretical overview and practical example. *J Neurosci Methods*, 2022, **371**: 109494
- [46] Strafella R, Momi D, Zomorodi R, *et al.* Identifying neurophysiological markers of intermittent theta burst stimulation in treatment-resistant depression using transcranial magnetic stimulation-electroencephalography. *Biol Psychiatry*, 2023, **94**(6): 454-465
- [47] Biermann L, Wunram H L, Pokorny L, *et al.* Changes in the TMS-evoked potential N100 in the dorsolateral prefrontal cortex as a function of depression severity in adolescents. *J Neural Transm (Vienna)*, 2022, **129**(11): 1339-1352
- [48] Voineskos D, Blumberger D M, Rogasch N C, *et al.* Neurophysiological effects of repetitive transcranial magnetic stimulation (rTMS) in treatment resistant depression. *Clin Neurophysiol*, 2021, **132**(9): 2306-2316
- [49] Cash R F, Noda Y, Zomorodi R, *et al.* Characterization of glutamatergic and GABA_A-mediated neurotransmission in motor and dorsolateral prefrontal cortex using paired-pulse TMS-EEG. *Neuropsychopharmacology*, 2017, **42**(2): 502-511
- [50] Noda Y, Cash R F, Zomorodi R, *et al.* A combined TMS-EEG study of short-latency afferent inhibition in the motor and dorsolateral prefrontal cortex. *J Neurophysiol*, 2016, **116**(3): 938-948
- [51] Garcia-Larrea L, Peyron R. Pain matrices and neuropathic pain matrices: a review. *Pain*, 2013, **154**: S29-S43
- [52] Premoli I, Castellanos N, Rivolta D, *et al.* TMS-EEG signatures of GABAergic neurotransmission in the human cortex. *J Neurosci*, 2014, **34**(16): 5603-5612
- [53] Premoli I, Rivolta D, Espenhahn S, *et al.* Characterization of GABAB-receptor mediated neurotransmission in the human cortex by paired-pulse TMS-EEG. *Neuroimage*, 2014, **103**: 152-162
- [54] Darmani G, Bergmann T O, Zipser C, *et al.* Effects of antiepileptic drugs on cortical excitability in humans: a TMS-EMG and TMS-EEG study. *Hum Brain Mapp*, 2019, **40**(4): 1276-1289
- [55] Parker R S, Lewis G N, Rice D A, *et al.* Is motor cortical excitability altered in people with chronic pain? A systematic review and meta-analysis. *Brain Stimul*, 2016, **9**(4): 488-500
- [56] Androulakis X M, Krebs K A, Jenkins C, *et al.* Central executive and default mode network intranet work functional connectivity patterns in chronic migraine. *J Neurol Disord*, 2018, **6**(5): 393
- [57] Rogasch N C, Zipser C, Darmani G, *et al.* The effects of NMDA receptor blockade on TMS-evoked EEG potentials from prefrontal and parietal cortex. *Sci Rep*, 2020, **10**(1): 3168
- [58] Sanchez-Vives M V, Barbero-Castillo A, Perez-Zabalza M, *et al.* GABA_B receptors: modulation of thalamocortical dynamics and synaptic plasticity. *Neuroscience*, 2021, **456**: 131-142
- [59] Tracey I, Mantyh P W. The cerebral signature for pain perception and its modulation. *Neuron*, 2007, **55**(3): 377-391
- [60] Tang Y T, Li Y H, Shen X B, *et al.* The neural oscillatory mechanisms of emotion affecting working memory: a dual-path model based on competition and interference. *Prog Biochem Biophys*, 2026, **53**(1): 117-129
- [61] Vogt B A. Midcingulate cortex: structure, connections, homologies, functions and diseases. *J Chem Neuroanat*, 2016, **74**: 28-46
- [62] Ye Y, Wang J, Che X. Concurrent TMS-EEG to reveal the neuroplastic changes in the prefrontal and insular cortices in the analgesic effects of DLPFC-rTMS. *Cereb Cortex*, 2022, **32**(20): 4436-4446
- [63] ter Braack E M, de Vos C C, van Putten M J. Masking the auditory evoked potential in TMS-EEG: a comparison of various methods. *Brain Topogr*, 2015, **28**(3): 520-528
- [64] Duecker F, Sack A T. Rethinking the role of sham TMS. *Front Psychol*, 2015, **6**: 210
- [65] Gordon P C, Song Y F, Jovellar D B, *et al.* Untangling TMS-EEG responses caused by TMS versus sensory input using optimized sham control and GABAergic challenge. *J Physiol*, 2023, **601**(10): 1981-1998
- [66] Kurth F, Zilles K, Fox P T, *et al.* A link between the systems: functional differentiation and integration within the human insula revealed by meta-analysis. *Brain Struct Funct*, 2010, **214**(5/6): 519-534
- [67] Cerliani L, Thomas R M, Jbabdi S, *et al.* Probabilistic tractography

- recovers a rostrocaudal trajectory of connectivity variability in the human insular cortex. *Hum Brain Mapp*, 2012, **33**(9): 2005-2034
- [68] Baydın Ş S, Barut O, Küçükyörük B, *et al.* Anatomical segmentation and connectivity of the uncinate fasciculus. *Turk Neurosurg*, 2025, 2012, **35**(4): 652-660
- [69] van Hattem T, Chang K Y, Tik M, *et al.* Contralateral prefrontal and network engagement during left DLPFC 10 Hz rTMS: an interleaved TMS-fMRI study in healthy adults. *Neuroimage Clin*, 2025, **48**: 103862
- [70] Fu Y, Long Z, Luo Q, *et al.* Functional and structural connectivity between the left dorsolateral prefrontal cortex and insula could predict the antidepressant effects of repetitive transcranial magnetic stimulation. *Front Neurosci*, 2021, **15**: 645936
- [71] Mainero C, Boshyan J, Hadjikhani N. Altered functional magnetic resonance imaging resting-state connectivity in periaqueductal gray networks in migraine. *Ann Neurol*, 2011, **70**(5): 838-845
- [72] Cash R F H, Cocchi L, Lv J, *et al.* Functional magnetic resonance imaging-guided personalization of transcranial magnetic stimulation treatment for depression. *JAMA Psychiatry*, 2021, **78**(3): 337-339
- [73] Cash R F, Zalesky A. Neuroimaging informed TMS and personalized targeting: evidence, controversies and opportunities. *Biol Psychiatry*, 2023, **95**(6): 463-475
- [74] Morris R, Briley P M, Webster L, *et al.* Connectivity-guided intermittent theta burst versus repetitive transcranial magnetic stimulation for treatment-resistant depression: a randomized controlled trial. *Nat Med*, 2024, **30**(2): 403-413
- [75] Motzkin J C, Kanungo I, D'Esposito M, *et al.* Network targets for therapeutic brain stimulation: towards personalized therapy for pain. *Front Pain Res (Lausanne)*, 2023, **4**: 1156108
- [76] Bai Y, Pacheco-Barrios K, Pacheco-Barrios N, *et al.* Neurocircuitry basis of motor cortex-related analgesia as an emerging approach for chronic pain management. *Nat Ment Health*, 2024, **2**(5): 496-513
- [77] Cole E, Phillips A, Bentzley B, *et al.* A double-blind, randomized, sham-controlled trial of accelerated intermittent theta-burst (aiTBS) for treatment-resistant depression. *Biol Psychiatry*, 2021, **89**(9): S90
- [78] Cole E J, Phillips A L, Bentzley B S, *et al.* Stanford neuromodulation therapy (SNT): a double-blind randomized controlled trial. *Am J Psychiatry*, 2022, **179**(2): 132-141
- [79] Zhao H, Jiang C, Zhao M, *et al.* Comparisons of accelerated continuous and intermittent theta burst stimulation for treatment-resistant depression and suicidal ideation. *Biol Psychiatry*, 2024, **96**(1): 26-33
- [80] Che X, Zhao H, Ye X, *et al.* Frontoparietal network mediates the antidepressant effects of accelerated iTBS and cTBS: TMS-EEG study. *Cell Rep Med*, 2025, **6**(12): 102470
- [81] Modir J G, Wallace M S. Human experimental pain models 2: the cold pressor model//Szallasi A. *Analgesia: Methods and Protocols*. Totowa, NJ: Humana Press, 2010: 165-168
- [82] Richardson H L, Macey P M, Kumar R, *et al.* Neural and physiological responses to a cold pressor challenge in healthy adolescents. *J Neurosci Res*, 2013, **91**(12): 1618-1627
- [83] Schwedt T J, Schlaggar B L, Mar S, *et al.* Atypical resting-state functional connectivity of affective pain regions in chronic migraine. *Headache*, 2013, **53**(5): 737-751
- [84] Pascual-Leone A, Freitas C, Oberman L, *et al.* Characterizing brain cortical plasticity and network dynamics across the age-span in health and disease with TMS-EEG and TMS-fMRI. *Brain Topogr*, 2011, **24**(3/4): 302-315
- [85] Stewart W F, Wood C, Reed M L, *et al.* Cumulative lifetime migraine incidence in women and men. *Cephalalgia*, 2008, **28**(11): 1170-1178
- [86] Hill A T, Rogasch N C, Fitzgerald P B, *et al.* Effects of prefrontal bipolar and high-definition transcranial direct current stimulation on cortical reactivity and working memory in healthy adults. *Neuroimage*, 2017, **152**: 142-157
- [87] Casula E P, Rocchi L, Hannah R, *et al.* Effects of pulse width, waveform and current direction in the cortex: a combined cTMS-EEG study. *Brain Stimul*, 2018, **11**(5): 1063-1070
- [88] Luo X, Che X, Li H. Concurrent TMS-EEG and EEG reveal neuroplastic and oscillatory changes associated with self-compassion and negative emotions. *Int J Clin Health Psychol*, 2023, **23**(1): 100343
- [89] Pascarella A, Mikulan E, Sciacchitano F, *et al.* An *in-vivo* validation of ESI methods with focal sources. *Neuroimage*, 2023, **277**: 120219
- [90] Hernandez-Pavon J C, Veniero D, Bergmann T O, *et al.* TMS combined with EEG: recommendations and open issues for data collection and analysis. *Brain Stimul*, 2023, **16**(2): 567-593
- [91] Conde V, Tomasevic L, Akopian I, *et al.* The non-transcranial TMS-evoked potential is an inherent source of ambiguity in TMS-EEG studies. *NeuroImage*, 2019, **185**: 300-312
- [92] Song Y, Gordon P C, Metsomaa J, *et al.* Evoked EEG responses to TMS targeting regions outside the primary motor cortex and their test-retest reliability. *Brain Topogr*, 2024, **37**(1): 19-36
- [93] Gao M, Wong N M L, Lin C, *et al.* Multimodal brain connectome-based prediction of suicide risk in people with late-life depression. *Nat Ment Health*, 2023, **1**(2): 100-113
- [94] Chen H L, Li Q, Li Y Y, *et al.* Regulation of social interaction through transcranial electrical stimulation-based multibrain stimulation. *Prog Biochem Biophys*, 2026, **53**(1): 105-116
- [95] Duan H Q, Gou Y Q, Li Y W, *et al.* The potential and challenges of temporal interference stimulation in chronic pain management. *Prog Biochem Biophys*, 2026, **53**(2): 369-387

背外侧前额叶皮层重复经颅磁刺激治疗偏头痛的神经环路特征*

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摘要 **目的** 偏头痛是全球范围内导致健康寿命损失的主要疾病之一。通过作用于背外侧前额叶皮层, 重复经颅磁刺激技术为偏头痛患者提供了一种安全且前景广阔的治疗方案。然而, 重复经颅磁刺激改善偏头痛症状的具体作用机制尚不明确, 阐明该机制对提升其临床疗效具有重要指导意义。**方法** 本研究采用经颅磁刺激-脑电图同步记录技术, 旨在揭示重复经颅磁刺激治疗偏头痛的神经可塑性及神经环路机制。研究一对比偏头痛患者(30例)与健康受试者(28例), 探查其神经可塑性与神经环路活动的异常特征; 研究二则在34例健康受试者中观察重复经颅磁刺激对这些异常特征及疼痛体验的调节作用。**结果** 偏头痛患者存在以N120波幅为指标的局部神经可塑性异常, 且在初级躯体感觉皮层、后脑岛、前脑岛及中扣带皮层等疼痛处理脑区表现出异常升高的显著电流密度。单次背外侧前额叶重复经颅磁刺激干预可降低初级躯体感觉皮层、前脑岛及中扣带回的显著电流密度, 且初级躯体感觉皮层和中扣带回的神经活动与疼痛感知程度呈相关性。**结论** 本研究从神经可塑性与神经环路两个维度为重复经颅磁刺激治疗偏头痛的机制提供了实证依据, 这有助于深入理解其治疗原理, 并为开发更有效的偏头痛治疗方案提供指导。

关键词 偏头痛, 经颅磁刺激, 背外侧前额叶皮层, 经颅磁刺激-脑电图同步记录

中图分类号 R747.2, R741.044, R318.04

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